AMENDMENTS TO THE SPECIFICATION

Please replace the paragraph bridging pages 8 and 9 of the specification with the following amended paragraph:

It is an object of the present invention to discover genes having a novel function of regulating cartilage differentiation and to use such genes for diagnosing, regulating, and treating a bone and/or joint disease such as osteoarthritis. Such genes can be obtained by focusing on the Runx2/Cbfa1 transcription factor deeply associated with a bone and/or joint disease, i.e., osteoarthritis, and introducing Runx2/Cbfa1 into Runx2/Cbfa1-deficient mouse-derived primary chondrocytes or ~~Runx2/Cba1~~Runx2/Cbfa1- and p53-deficient mouse-derived chondrocyte cell lines to identify the genes the expressions of which are thereby induced. Further, an object of the present invention is to provide polypeptides encoded by the aforementioned genes, antibodies against such polypeptides, transgenic animals for such genes, and animal models of a bone and/or joint disease (preferably osteoarthritis). It is another object of the present invention to screen for compounds that regulate the functions or expression of the aforementioned polypeptides using the aforementioned objects. Furthermore, an object of the present invention is to provide compounds selected by screening, a means for diagnosing diseases and therapeutic agents using the same.

Please insert the following paragraph on page 13 (line 23) of the specification:

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawings will be provided by the Office upon request and payment of the necessary fee.

Please replace the second paragraph (lines 8-22) on page 24 of the specification with the following amended paragraph:

The polynucleotides of the genes the expressions of which are induced by Runx2/Cbfa1 identified above (the left column in Table 1) are derived from mice. Human homologues thereof can be easily identified by searching public databases. The nucleotide sequences of the human homologues identified by searching of public databases (e.g., the ~~GenBank~~GENBANK™ database) are shown in SEQ ID NOs: 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, and 51 (the right column in Table 1). Human homologues can also be identified via homology search of public databases. In such a case, human homologues can be identified by selecting genes encoding proteins that are most homologous to the polypeptides encoded by the aforementioned genes, from among the genes encoding proteins having 60% or more, and preferably 65% or more, homology to such polypeptides. Homology search of proteins is known in the art, and homology can be easily determined with the use of, for example, a known protein homology search program, i.e., BLAST (Altschul S.F. et al., 1990, Basic local alignment search tool, J. Mol. Biol. 215: 403-410; and Karlin S. and Altschul S.F., 1990, Proc. Natl. Acad. Sci. U.S.A., 87: 2264-2268).

Please replace the third paragraph (lines 14-25) on page 32 of the specification with the following amended paragraph:

The present invention relates to the Runx2/Cbfa1-deficient mouse-derived primary cultured chondrocytes or cultured chondrocytes or ~~Runx2/Cba1~~Runx2/Cbfa1- and p53-deficient mouse-derived chondrocyte cell lines that can be employed for the aforementioned technique for searching for a gene. The Runx2/Cbfa1-deficient mouse-derived primary cultured chondrocytes

are obtained by treating the skeleton of a Runx2/Cbfa1-deficinet mouse at day 18.5 of embryonic development with trypsin and collagenase. The ~~Runx2/Cba1~~Runx2/Cbfa1- and p53-deficient mouse-derived chondrocyte cell lines were established by treating the skeleton of a ~~Runx2/Cba1~~Runx2/Cbfa1- and p53-deficient mouse at day 18.5 of embryonic development with trypsin and collagenase, and repeating cloning 3 or 4 times. Methods for establishing the aforementioned primary chondrocytes and chondrocyte cell lines are known, and such cells or cell lines can be obtained in accordance with other conventional techniques.

Please replace the paragraph bridging pages 32 and 33 of the specification with the following amended paragraph:

Preferable examples of ~~Runx2/Cba1~~Runx2/Cbfa1- and p53-deficient mouse-derived chondrocyte cell lines include, but are not limited to, RU-1 and RU-22. The RU-1 and RU-22 cell lines are deposited at the International Patent Organism Depositary of the National Institute of Advanced Industrial Science and Technology (Tsukuba Central 6, 1-1-1 Higashi, Tsukuba, Ibaraki-ken, 305-8566 Japan) under the Budapest Treaty as of August 5, 2003 (the original deposit), under the accession numbers FERM BP-10137 (the RU-1 cell line) and FERM BP-10138 (the RU-22 cell line).

Please replace the first full paragraph (lines 13-27) on page 62 of the specification with the following amended paragraph:

In order to examine the differentiation stage and properties of the resulting cell lines, the expression patterns of type II collagen and type X collagen in RU-22 and in RU-1 were analyzed via real-time PCR. The RU-22 and RU-1 cell lines were cultured in 10% fetal bovine

serum/Dulbecco's Modified Eagle's Medium (DMEM), and total RNA was purified using ~~Isogen~~ISOGEN™ (Nippon Gene) when the cells became confluent. Total RNA was prepared in accordance with the method described in the instructions of ~~Isogen~~ISOGEN™. Further, single-stranded cDNA was synthesized from total RNA using a reverse transcriptase and an oligo (dT) primer. The resultant was used as a template to assay the expression level of type II collagen and type X collagen via real-time PCR analysis. Assay was conducted using the ABI PRISM 7700™ (Applied Biosystems) in accordance with the instructions of the SYBR™ Green PCR Master Mix (Applied Biosystems). The sequences of the primers used are shown in Table 2. The Ct values obtained as a result of the assay were corrected with the expression of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and expressed as the relative value when GAPDH was determined to be 1,000 (Fig. 2).

Please replace the third paragraph (lines 14-23) on page 68 of the specification with the following amended paragraph:

The RU-1 and RU-22 cell lines were plated onto 10 wells of the 12-well collagen-coated plate, they were cultured to be confluent, and they were then infected with the adenovirus for the expression of Runx2/Cbfa1 and the control virus (for the expression of GFP only). One day after the injection, total RNA was recovered using ~~Isogen~~ISOGEN™ 1 and total RNA was prepared in accordance with the instructions of the reagent. Thereafter, poly A+ RNA was prepared using the ~~Oligotex~~OLIGOTEX™-dT30<Super>mRNA Purification Kit (Takara) in accordance with the instructions of the kit, and the resultant was employed as a sample for DNA microarray analysis. DNA microarray analysis was carried out using ~~LifeArray~~LIFEARRAY™ (Kurabo Industries Ltd.; the number of mouse genes: approximately 9,500).

Please replace the paragraph bridging pages 68 and 69 of the specification with the following amended paragraph:

The primary cultured chondrocytes derived from Runx2/Cbfa1-/- were plated onto 10 wells of the 12-well collagen-coated plate, they were cultured to be confluent, and they were then infected with the adenovirus for the expression of Runx2/Cbfa1 and the control virus (for the expression of GFP only). One day after the injection, total RNA was recovered using ~~Isogen~~ISOGEN™ I and total RNA was prepared in accordance with the instructions of the reagent. The resultant was employed as a sample for DNA microarray analysis. DNA microarray analysis was carried out using the ~~CodeLink~~ CODELINK™ DNA microarray (Kurabo Industries Ltd.; the number of mouse genes: approximately 10,000).

Please replace the first full paragraph (lines 9-17) on page 69 of the specification with the following amended paragraph:

Fig. 9 shows some genes the expressions of which are induced along with the forced expression of Runx2/Cbfa1, which were identified via DNA microarray analysis. With the use of the ~~LifeArray~~LIFEARRAY™, expression of alkaline phosphatase (ALP), which is known to be regulated by Runx2/Cbfa1, was found to be induced in each cell line and in primary cultured cells. This indicates that the performance of the experimental system is successful. With the use of the ~~CodeLink~~ CODELINK™ DNA microarray, the expression of alkaline phosphatase (ALP) and that of collagenase-3 (MMP-13), which are known to be induced by Runx2/Cbfa1, were found to be induced. This indicates that the performance of the experimental system is successful.